REMARKS/ARGUMENTS

Claims 1-14 and 48-49 were pending. Claim 7 is canceled. Claims 5, 8, 9, 13 and 49 are amended. Claims 1-6, 8-14 and 48-49 are currently under examination.

Claim Amendments

Claims 5, 8, 9, 13 and 49 are amended so that they are in independent form and no longer depend from a rejected independent claim.

Claim 8 is further amended to clarify the claimed subject matter. Support for the amended Claim 8 can be found in the original claims 1 and 8, and in the published Specification at least at Paragraphs [0001], [0024] and [0046].

Claim 13 is further amended to delete surplus language. Support for the amended claim can be found in the original claims 1, 11 and 12, and in the Specification at least at Paragraphs [0021] and [0022].

Applicants respectfully submit that no new matter has been added by the amendments.

Claim Rejections – 35 U.S.C. § 103

Claims 1-4, 11 and 48 were rejected under 35 U.S.C. 103(a) for obviousness reasons over Hansen (WO 91/08770, 1991) and Barbet (U.S. 5,256,395, 1993). Applicants respectfully traverse this rejection and submit that Claim 1 is not obvious over Hansen and Barbet.

A prima facie case of obviousness requires three elements: (1) a teaching or suggestion of all of the claim limitations; (2) a suggestion or motivation to modify or combine the teachings of the applied prior art; and (3) a reasonable expectation of success in reaching the claimed invention. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that each of the requirements is lacking here.

First, neither Hansen no Barbet disclose the element "wherein one arm of the bispecific antibody is targeted against a target site antigen and a second arm is targeted against a low molecular weight hapten that is conjugated to said enzyme, and administering a low molecular weight hapten that is conjugated to said enzyme."

Hansen discloses a bispecific antibody wherein one arm of the antibody is either directly conjugated to the enzyme being targeted or is specific against the enzyme being targeted. In contrast, the instant claimed subject matter discloses a bispecific antibody that is specific *against a small molecular weight hapten* to which *any* enzyme can be linked. Therefore, the Hansen invention requires construction of a different bi-specific antibody for each intended enzyme [See Hansen Specification at paragraph [0005] "its adoption with different combinations of prodrugs and enzymes would require the preparation of new bsMAbs for each combination"], whereas the instant claimed invention provides for construction of a single bispecific antibody that can achieve pretargeting of numerous enzymes.

Barbet discloses a bispecific antibody that is specific against a low molecular weight hapten. However, in Barbet the hapten is conjugated *not to the targeting enzyme*, but to a therapeutic agent such as a radioactive isotope, paramagnetic ion, drug or toxin. [See Barbet at Column 4, lines 43-67; Column 5 lines 38-41; Column 6, line 67 - Column 8, line 18]. In contrast, in the instant claimed subject matter, the hapten is conjugated to the enzyme and the therapeutic agent is administered separately. This has the advantage of localizing the enzyme at the target site, so that the conversion of the detoxified therapeutic agent into its toxic form occurs at the target site and results in an increased active drug concentration at the target site. [See published Specification at paragraph [0003] "the targeted enzyme activity [affords] the ability to produce large amounts of drug where it is needed"]. Barbet does not teach nor recognize such advantages of using a hapten-enzyme conjugate to target an enzyme. Furthermore, Barbet teachings cannot be used to construct a hapten-enzyme conjugate. The design requirements disclosed are for constructing hapten-therapeutic agent conjugates, which are not suitable for constructing hapten-enzyme conjugates. Specifically, Barbet teaches linking at least two haptens to the therapeutic agent for effecting affinity enhancement [See Barbet at Column 4, lines 48-50], and the methods]See Barbet Examples 2 and 3] require use of organic solvents, and strong acidic and basic conditions. These methods cannot be used for preparing hapten-enzyme conjugates due to concerns over denaturing the enzyme. Thus, neither Barbet, nor Hansen disclose a hapten conjugated to enzyme.

Second, neither Hansen, nor Barbet disclose the element of "administering a cytotoxic chemotherapeutic agent known to act at the target site, or a prodrug form thereof which is converted to the chemotherapeutic agent in situ, which chemotherapeutic agent is also detoxified

to form an intermediate of lower toxicity using said mammal's ordinary metabolic processes, whereby the detoxified intermediate is reconverted to its more toxic form by the pretargeted enzyme and thus has enhanced cytotoxicity at the target site." The Action on page 5 states that "while Hansen does not explicitly teach that the epirubicin in detoxified to form an intermediate of lower toxicity, whereby the detoxified intermediate is reconverted to its more toxic form by the pretargeted enzyme, the claimed limitation does not appear to result in a manipulative difference in the method steps . . ." Applicants respectfully disagree. The Hansen method specifically requires preparation and administration of a glucuronide derivative of the drug [See Hansen at Page 13, line 19 – Page 14, line 35; Page 34, Example 3] whereas the claimed subject matter teaches administration of an *unaltered*, cytotoxic form of the drug, which then may be converted to a glucuronide by the body's internal detoxifying mechanism. Thus, Hansen requires the additional steps of preparation of glucuronide prior to administration, which is not required in the claimed subject matter. Thus, this element is also not disclosed in Hansen or Barbet.

Furthermore, neither Hansen, nor Barbet contain any suggestion or motivation to modify or combine their respective teachings, and based on their disclosures a skilled artisan would not have any expectation of success in reaching the claimed subject matter. The claimed invention looks obvious only in hindsight and such hindsight construction is impermissible. Therefore, applicants respectfully request reconsideration and withdrawal of the rejection of Claim 1 over Hansen and Barbet.

Since Claims 2-4, 11 and 48 depend from Claim 1, and include all limitations of Claim 1 plus additional limitations, these claims are also not obvious over Hansen and Barbet. Applicants respectfully request that these claims be allowed as well.

Claims 12 and 14 were rejected over Hansen, Barbet and Griffiths (WO 96/40245, 1996). Griffiths teaches the administration of a clearing agent, but Griffiths does not teach the above discussed elements of Claim 1. Since Claims 12 and 14 depend from Claim 11, which in turn depends from Claim 1, for the above stated reasons applicants submit that rejection of these claims should also be withdrawn.

Claim objections

Examiner had indicated that claims 5-6, 8-10, 13, and 49 were free from prior art and would be allowable if written in independent form. Applicants have amended Claims 5, 8, 9, 13 and 49 so that they are in independent form and are allowable. Since Claims 6 and 10 depend from amended independent Claims 5 and 8, they are also allowable.

Conclusion

For the reasons stated above, Applicants submit that the amended claims are in condition for allowance and request withdrawal of the rejections.

Respectfully submitted,

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